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Arrhythmia prophylaxis after coronary artery surgery

A randomised controlled trial of intravenous magnesium chloride

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Abstract. One hundred and thirty patients undergoing elective myocardial revascularisation were randomised to receive an intravenous infusion containing either 50 mmol magnesium chloride or placebo during the first 48 h following surgery. Magnesium was given to 66 patients and a placebo infusion to 64 patients. Postoperative serum magnesium concentrations fell in the placebo group (from 0.83 ± 0.06 to 0.79 ± 0.11 mmol/l) but were elevated in the magnesium group (from 0.82 ± 0.05 to 1.2 ± 0.25 mmol/l). In total, 35 patients (26.9%) had a supraventricular arrhythmia, of which 11 were in the magnesium group (16.7%) and 24 (37.5%) in the placebo group (P = 0.013). Three patients in the magnesium group had an episode of ventricular fibrillation and three patients in the placebo group had frequent ventricular ectopics. There was one death in the magnesium group associated with a perioperative myocardial infarction. This study shows that intravenous magnesium supplements reduce the incidence of supraventricular arrhythmias following coronary artery surgery. [Eur J Cardio-thorac Surg (1993) 7:520–523]

Key words: Arrhythmias – Coronary artery surgery – Magnesium

Supraventricular tachyarrhythmias occur frequently following coronary artery surgery and, although not usually life-threatening, they constitute significant morbidity and can prolong hospital stay [21, 25]. Various regimes involving both preoperative and postoperative digitalisation or beta-blockade have shown equivocal results in the prophylaxis of arrhythmic events [19, 25]. The high incidence of arrhythmias seen during the first 48 h following an acute myocardial infarction is thought to be related to a transient fall in serum magnesium levels which occurs during this time [5, 22]. There have been several studies which have addressed the issue of intravenous magnesium therapy following acute myocardial infarction [1, 4, 12, 23, 24, 28, 29] and the overall consensus is that magnesium reduces both the number of arrhythmic events and early mortality [30]. Serum magnesium concentrations are also known to fall during cardiopulmonary bypass and remain low for 3–5 days following surgery [13, 17, 26]. Hence this prospective study was performed to investigate the effects of intravenous magnesium on the prevention of arrhythmias following coronary artery surgery.

Material and methods

One hundred and thirty consecutive patients undergoing elective coronary artery surgery were studied in this prospective double-blind controlled trial. The study was approved by the Glasgow Royal Infirmary Ethical Committee. Patients were excluded from the study if they were not in sinus rhythm or were taking anti-arrhythmic medication. Patients with biochemical evidence of impaired renal function (serum creatinine more than 130 mmol/l and/or urea more than 15 mmol/l) and those taking medication which contained magnesium were also excluded. All patients underwent myocardial revascularisation with cardiopulmonary bypass, moderate systemic hypothermia, topical hypothermia and either blood cardioplegia or St Thomas No 1 cardioplegic solution.

Informed consent was obtained from all patients, who were randomised to receive either an intravenous infusion containing magnesium chloride or placebo following surgery. The trial was designed to allow the administration of magnesium or placebo in the routine maintenance fluids. In the first 24 h following surgery one ampoule, containing either placebo or 20 mmol of magnesium chloride, was added to each 500 ml bag of 5% dextrose and infused at 40 ml/h (1.6 mmol magnesium chloride per hour). During the second 24 h period one ampoule, containing either placebo or
10 mmol of magnesium chloride, was added to a 500 ml bag of dextrose so that patients in the magnesium group received a total of 50 mmol of magnesium chloride over 48 h. During this period serum potassium was maintained at 4.5–5.0 mmol/l in all patients by regular serum analysis and supplementation if necessary.

Magnesium was determined in serum and urine by a standard flame atomic absorption method, samples being diluted with 0.5% LaCl3 prior to analysis. The precision of the method was checked by three pools of serum with low (0.41 mmol/l), medium (0.78 mmol/l) or high (1.5 mmol/l) magnesium concentration and the average coefficient of variation of the samples was 1.8%. External quality control samples were analysed with each batch of samples and yielded similar satisfactory results.

The electrocardiogram (ECG) was monitored continuously during the first 24 h period. A 12-lead ECG recording was made on the first, second, third and fifth postoperative days. A further recording was made if there was clinical suspicion of an arrhythmia as suggested by a pulse rate less than 60 or greater than 110 beats per minute, an irregular pulse rate, hypotension or a deterioration in the patient’s clinical condition. Atrial fibrillation, atrial flutter, frequent atrial ectopics or supraventricular tachycardia was recorded as an arrhythmic event if it was sustained for more than 30 s. Episodes of ventricular fibrillation, ventricular tachycardia and premature ventricular extrasystoles (greater than five per minute, multifocal or bigeminal) were also recorded as arrhythmic events. If a patient had several types of supraventricular arrhythmia the first arrhythmia only was counted as an arrhythmic episode. All arrhythmias in the study required further treatment. Data is reported as the mean ± standard deviation. Data was analysed by analysis of variance, the chi-square test and with the paired or unpaired t-test where appropriate.

Results

The code for administration of magnesium or placebo was broken following completion of the study. Magnesium was given to 66 patients and a placebo infusion to 64 patients. There were no preoperative differences between the groups regarding age, sex, previous myocardial infarction, diabetes, hypertension, anti-anginal medication or diuretic therapy (Table 1). There was also no difference between the groups regarding the operative variables of bypass time, ischaemic time, the number of bypass grafts, the type of cardioplegia used or the postoperative use of inotropes (Table 2). The overall use of inotropes was 21/66 in the magnesium group (31.8%) and 22/64 in the control group (34.4%). The numbers and types of arrhythmias are shown in Table 3. In the magnesium group 11 patients (16.7%) had a supraventricular arrhythmia compared with 24 patients (37.5%) in the placebo group (P = 0.013). Three patients in the magnesium group had an episode of ventricular fibrillation and three patients in the placebo group had frequent ventricular ectopics. There were no statistically significant differences between the groups for the different ventricular arrhythmias. There was one hospital death (0.8%). This patient, who was in the magnesium group, had an episode of ventricular fibrillation 12 h postoperatively and was subsequently found to have an occluded vein graft and an acute inferior myocardial infarction. The patient died on the 20th postoperative day of multiorgan failure. No biochemical cause or evidence of myocardial infarction was identified in the other two patients who developed early unheralded ventricular fibrillation.

Table 1. Comparison of preoperative patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Magnesium group n = 66</th>
<th>Control group n = 64</th>
<th>Significance value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.1 ± 8.4</td>
<td>58.7 ± 7.9</td>
<td>0.253</td>
</tr>
<tr>
<td>Male</td>
<td>55 (83.3%)</td>
<td>51 (79.7%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>30 (45.5%)</td>
<td>34 (53.1%)</td>
<td>0.484</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (6.1%)</td>
<td>2 (3.1%)</td>
<td>0.704</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (24.2%)</td>
<td>14 (21.9%)</td>
<td>0.911</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>46 (69.7%)</td>
<td>41 (64.1%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>54 (81.8%)</td>
<td>52 (81.2%)</td>
<td>0.887</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>57 (78.8%)</td>
<td>52 (81.2%)</td>
<td>0.895</td>
</tr>
<tr>
<td>Diuretics</td>
<td>7 (10.6%)</td>
<td>14 (21.9%)</td>
<td>0.129</td>
</tr>
</tbody>
</table>

Table 2. Comparison of operative and postoperative characteristics

<table>
<thead>
<tr>
<th></th>
<th>Magnesium group</th>
<th>Control group</th>
<th>Significance value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic time (min)</td>
<td>51.5 ± 18.1</td>
<td>51.7 ± 19</td>
<td>0.952</td>
</tr>
<tr>
<td>Bypass time (min)</td>
<td>85.7 ± 27.2</td>
<td>86.7 ± 28.4</td>
<td>0.833</td>
</tr>
<tr>
<td>Number of grafts</td>
<td>3.04 ± 0.97</td>
<td>3.3 ± 0.92</td>
<td>0.132</td>
</tr>
<tr>
<td>Internal mammary artery</td>
<td>57 (86.4%)</td>
<td>61 (95.3%)</td>
<td>0.144</td>
</tr>
<tr>
<td>Crystallloid cardioplegia</td>
<td>56 (84.9%)</td>
<td>55 (85.9%)</td>
<td>0.942</td>
</tr>
<tr>
<td>Blood cardioplegia</td>
<td>10 (15.1%)</td>
<td>9 (14.1%)</td>
<td>0.942</td>
</tr>
<tr>
<td>Dopamine</td>
<td>10 (15.8%)</td>
<td>16 (25%)</td>
<td>0.236</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>8 (12%)</td>
<td>4 (6%)</td>
<td>0.394</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>3 (4.5%)</td>
<td>2 (3.1%)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Table 3. Postoperative supraventricular and ventricular arrhythmias. The first clinically significant atrial arrhythmia only was counted as an arrhythmic event

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Magnesium group n = 66</th>
<th>Control group n = 64</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>11</td>
<td>15</td>
<td>0.013</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial ectopics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular ectopics</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraventricular arrhythmias</td>
<td>11</td>
<td>24</td>
<td>0.0013</td>
</tr>
<tr>
<td>Statistical significance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All arrhythmias</td>
<td>14</td>
<td>25*</td>
<td>0.042</td>
</tr>
<tr>
<td>Statistical significance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Two patients had ventricular and supraventricular arrhythmias.
shortly after transfer from theatre to the intensive care unit. The changes in serum magnesium concentrations and urinary magnesium excretion are shown in Table 4. Postoperative serum magnesium concentrations fell in the control group from 0.83 ± 0.06 to 0.77 mmol/l ± 0.11 mmol/l on the second postoperative day (P = 0.00001) but were elevated in the magnesium group from 0.82 ± 0.05 mmol/l to 1.2 ± 0.25 mmol/l (P = 0.00001). Both groups showed an increase in urinary excretion of magnesium postoperatively, which was quite marked in the magnesium group.

Discussion

This study showed a significant reduction of supraventricular arrhythmias in a group of patients who were given an intravenous infusion of magnesium following coronary artery surgery. The patients in the control group, who had an incidence of supraventricular arrhythmias comparable with other studies [21, 25], had a fall in their serum magnesium concentrations during the first two postoperative days. In animals low serum magnesium levels are associated with cardiac arrhythmias [7, 8, 20, 27], an increase in catecholamine-induced myocardial necrosis [20] and coronary artery spasm [2, 31]. The coronary artery spasm may be due to an increased response to vasoconstrictors such as potassium, angiotensin and noradrenaline [31]. Low serum magnesium concentrations in man are also associated with coronary artery spasm and sudden cardiac death [9, 23] although it is difficult to separate these effects from an associated potassium deficiency. Although hypomagnesaemia may not be the primary cause of arrhythmias following an acute myocardial infarction, the effectiveness of magnesium treatment for this condition and the knowledge that hypomagnesaemia occurs following open heart surgery led us to conduct this study. In our patients the serum magnesium concentrations and urinary magnesium output did not suggest nutritional magnesium deficiency.

The amount of magnesium given to the patients in this study is comparable to the amount given in previous studies for the prophylaxis of arrhythmias following an acute myocardial infarction [22, 24, 28, 29]. These studies also showed a similar rise of the mean concentrations of serum magnesium in the treated groups to between 1.0 and 1.5 mmol/l. The mechanism of magnesium’s anti-dysrhythmic action remains unknown but appears to be irrespective of the serum magnesium level [14, 16] and may be due to several effects [33]. Increasing extracellular magnesium concentrations may limit damage by inhibiting calcium influx into myocardial cells [15]. In animal studies magnesium was shown to increase the threshold for electrical excitation of myocardial cells and so reduce the likelihood that an injury current will create an abnormal focus of excitation near the ischaemic tissue [7].

Animal studies have shown that magnesium is beneficial when added to cardioplegic solutions. When magnesium was included in cardioplegic solutions an increase in contractility and decrease in the amount of arrhythmias was seen after reperfusion [10, 32]. Since this study was initiated there has been a report of a similar trial of magnesium supplementation following coronary artery surgery [6]. Fanning et al. conducted a placebo-controlled trial with magnesium sulphate although their administration of magnesium was more complex, requiring an intravenous infusion over a 4-day period. However, their results were remarkably similar to ours, showing a reduction in the incidence of supraventricular arrhythmias with no change in ventricular arrhythmias. There have been several other studies that have addressed the issue of hypomagnesaemia in relation to cardiac surgery. In 1971, in a small study, Scheinman and colleagues added magnesium to the pump prime in one group of patients and compared their postoperative arrhythmias with those of a group of patients receiving no supplements. The authors found that patients who had received supplements required fewer shocks for cardiac defibrillation and had fewer postoperative arrhythmias although their results did not reach statistical significance [26]. Büky gave intravenous magnesium during reperfusion and found that defibrillation occurred spontaneously in two-thirds of the patients and ease of defibrillation was noted in the remaining cases [3]. Krasner gave patients slow-release oral magnesium tablets for 4 days preoperatively and found a decrease in the amount of postoperative arrhythmias and a reduction in the corrected QT interval [18]. There is only one publication which suggests that an infusion of magnesium may be detrimental [11]. Hecker et al. concluded that administration of intravenous magnesium before cardiopulmonary bypass could have adverse effects when plasma levels exceeded the mid-normal range. They found that patients who had received magnesium required higher energy levels to facilitate ventricular defibrillation. However, the number of patients studied was relatively small and none of their results reached statistical significance.

The contraindications to magnesium infusion following coronary artery surgery are few and the treatment regimes are safe, relatively inexpensive and can be easily managed. Magnesium therapy in non-surgical patients reduces mortality during the first few weeks following an acute myocardial infarction by between one-third and two-thirds [30]. Further trials would be required to investigate the effects of intravenous magnesium supplements on mortality following coronary artery surgery.
References

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